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10/045,721	10/26/2001	Naohiro Terada	5853-207	9675

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EXAMINER	
KELLY, ROBERT M	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/045,721	TERADA ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6 and 14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and argument of 9/6/07 are entered.

Claim 1 has been amended.

Claims 1, 3, 5, 6, and 14-20 are presently pending and considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of the amendments, the rejections of Claims 1, 3, 5, 6, and 14-20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn.

To wit, Applicant has now removed the lack of clarity for the test substances and their compositions and use.

Claim Rejections - 35 USC § 112 – new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 6, and 14-20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record, and as modified below for reasons necessitated by the amendments. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, from which all the other pending claims are dependent, and therefore encompass, encompasses a method for identifying any drug candidate for promoting tissue-specific differentiation of an embryonic stem cell into any type of cell, with specific method steps comprising a pre-culturing step for two days in hanging drops to produce embryoid bodies (step B) and a culturing step of at least about 5 days in, optionally, collagen coated plates (step c). Claims 3, 5, 6, and 14-20 are also rejected, as they do not modify the method in such a manner to allow possession, for the reasoning below.

Applicant only supports the claimed limitations in the form of providing antecedent basis for each of the limitations (Applicant's argument of 9/6/07, pp. 6-8). To wit, support is argued to be found for many different types of differentiated cell types in EXAMPLE 1 (e.g., Id., pp. 6-7, paragraph bridging), and further that hanging drops are taught in EXAMPLE 2 (e.g., Id., pp. 7-8), and that therefore, the combinations are disclosed as possessed (e.g., Id., pp. 6-8). However, the examples are considered to be implicit support for the claims, and such does not demonstrate the broad genera of differentiation into any cell type, as such is not further supported by any explicit disclosure, such that the Artisan would have understood that such a mix-and-match approach would be used. Such an approach would be, at best, supported by obviousness, however, the courts have made clear that obviousness does not substitute for possession.

The Examiner has reviewed the specification, and found that no explicit support for such a limitation exists, e.g., pp. 1-2, which provide the most explicit support for the claims, does not

teach culturing prior to addition of test substances for any specific time period, nor does it teach the use of collagen coated plates.

Hence, the specification provides no explicit support for the limitation. However, page 13 of the specification (paragraph 3), uses implicit disclosure of a specific experiment to show that EB bodies may differentiated from mouse ES cells after two days in hanging drop culture, and then performs 3 additional days in suspension culture, followed by more specific steps to be further differentiated under specific conditions into **hepatocytes** (pp. 13-16). Moreover, Applicant's equivalent to test substances were subsequently added, which are limited to specific growth factors (p. 16, paragraph 2).

Hence, at best, Applicant's disclosure relies on obviousness to produce the generic test method, and obviousness at the time of invention does not substitute for possession of the invention by Applicant at the time of invention.

Therefore, the Artisan could not determine that Applicant was in possession of a generic method to identify drug candidates for promoting generic tissue-specific differentiation of an ES cell, comprising the method claimed, except that method, limited to the steps and materials disclosed, as in page 13 of the specification, and which would further determine Applicant's disclosure to indicate that only heptocyte lineage cells were possessed.

Response to Argument – new matter

Applicant's argument 9/6/07 has been fully considered but is not found persuasive.

Applicant argues that Example 1 demonstrates a method for obtaining various cell types from ES cells, and that Example 2 demonstrates the same for obtaining hepatocyte cell types, and therefore, disclosure is provided for mixing-and-matching the various components (pp. 6-8).

Such is not persuasive. As shown above, the implicit disclosure simply does not evidence possession of the broad genera for any generic cell type differentiation and any method steps.

Hence, the rejection is maintained on modified basis, due to the amendments and for reasons of record.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of further consideration, and consultation with the Examiner's SPE and others, the rejections of Claims 1, 3, 5-6, and 14-20 under 35 U.S.C. 112, first paragraph, for lacking a fully enabling disclosure, are withdrawn.

To wit, it was discussed with the Examiner's SPE that the rejection is not the correct rejection, and instead, especially in light of KSR v. Teleflex, an obviousness rejection is the proper rejection to apply to these claims. Further to explain, in light of the Supreme Court's finding that specific motivation is no longer an issue in finding obviousness, it has been decided that the proper rejection is one of obviousness and in fact, the enablement rejection was improper.

Claim Rejections – 35 USC § 103 – Liu/Keller

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5 and 14-19 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO/10535 to Liu; Leahy, et al. (1999) J. Exp. Zoo., 284: 67-81; Angelov, et al. (1998) Developmental Neuroscience, 20(1): 42-51; and Tsung, et al. (1995) Shi Yan Sheng Wu Xue Bao, 28(2): 173-89 (ABSTRACT ONLY).

Claims 1, 3, 5, and 14-19 encompass a method to identify a drug candidate for promoting tissue-specific differentiation of an embryonic stem cell, comprising providing a library of at least 2 test substances, culturing the ES cells in at least 2 cultures for at least about 5 days in the absence of a test substance, contacting the cultures, separately, with either the first or second test substance, culturing for 4-18 additional days, and analyzing for increased tissue-specific gene expression. Claims 3 and 5 require the ES cells to be mammalian. Claims 14, 15, 16, 17, 18, and 19 requiring the analyzing the step to comprise isolating mRNA from the cultures, which is either isolating total RNA from the cultures or further requiring PCR to make cDNAs, using PCR, the mRNA is immobilized on a substrate, or the substrate is contacted with a probe which hybridizes to tissue-specific mRNA.

Although Liu does not define the steps contemplated by Applicant in the same manner as Applicant defines these steps, Liu obviates many of the limitations. Specifically, Liu discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell

gene associated with the differentiation ... of stem cells" (Liu, ABSTRACT). Such stem cells include ES cells (e.g., p. 6, paragraph 3). Liu teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, as well as those genes that are up-regulated in a tissue specific manner, and therefore, defines the markers that would be analyzed for increased specific gene expression. Further, Liu teaches comparison of the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore, would be associated with stem cell differentiation (Id., p. 5, lines 7-18; EXAMPLES 2-3). Moreover, Liu obviates the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in expression to take place, and hence, 7-18 days would be obtained depending on the specific lineage. Liu also teaches the aspects of mRNA isolation (p. 20), total cellular RNA isolation (p. 20), reverse transcription (p. 20), PCR amplification (pp. 23-24), immobilized mRNA (EXAMPLE 4), and probing for mRNA (EXAMPLE 4).

However, Liu does not teach or make obvious the prior step of culturing the cells for 5 days in the absence of a test substance or the use of mouse R1 ES cells. Nor does Liu teach the culturing of the ES cells by hanging drop for a period of 2 days to produce embryoid bodies.

On the other hand, Leahy teaches embryoid bodies can made of ES cells, which differentiate into various cells of the postimplantation embryo by culturing under specific

conditions for 5 days and up (p. 70). Moreover, Leahy teaches the addition of exogenous factors to increase differentiation of these embryoid bodies into specific lineages prior to screening for markers for differentiation of these cells into specific lineages (p. 80). Also, Leahy teaches that mouse R1 cells may be used (e.g., p. 68, col. 2, paragraph 2). Lastly, it is noted that Leahy teaches the days in suspension culture to differentiate the cells into other lineages, including up to 10 days, along with various markers which are expressed.

Still further, with regard to the shortened culturing and in hanging drops to produce such embryoid bodies, it is also well known in the Art that such embryoid bodies may be produced by culturing for two days (e.g., Angelov, et al. (1998) Developmental Neuroscience, 20(1): 42-51), and culturing may be done by hanging drop (e.g., Tsung, et al. (1995) Shi Yan Sheng Wu Xue Bao, 28(2): 173-89 (ABSTRACT ONLY)).

Hence, at the time of invention, it would have been obvious to modify the methods of Liu by using the methods of Leahy, Angelov, and Tsung to make embryoid bodies by hanging drop for two days, which are then screened for factors causing further differentiation of such cells to specific cell types. The Artisan would have been motivated to do so, as Liu had taught the screening method applicable to the cells, and Leahy had demonstrated the ability to make EB cells which can then form the various lineages. Moreover, the Artisan would have had a reasonable expectation of success, as Liu had taught the screening methods, and Leahy had demonstrated the ability to make the EB bodies and differentiate the ES cells to various types of cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5, 6, and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO/10535 to Liu; Leahy, et al. (1999) J. Exp. Zoo., 284: 67-81; Angelov, et al. (1998) Developmental Neuroscience, 20(1): 42-51); and Tsung, et al. (1995) Shi Yan Sheng Wu Xue Bao, 28(2): 173-89 (ABSTRACT ONLY)., as applied to claim 1 above, and further in view of US Pat No 5,874,301 to Keller, et al.

With regard to claim 1, the rejection is similarly obvious over Liu; Keller; Angelov; and Tsung, as shown above. However, they do not teach or make obvious the use of human ES cells.

On the other hand, Keller teaches isolated embryonic cell populations (TITLE), including ES cells (e.g., col. 5, paragraphs 5-6; col. 2, lines 5-8), which cells may be cultured prior to differentiation (e.g., col. 7, paragraph 1), which cells may be then used in differentiation experiments to derive various differentiated cell types (EXAMPLES). One such cell is the hepatocyte, which required culturing under appropriate conditions (i.e., differentiation conditions) for at least about 14 days (e.g., col. 20, paragraph 4). Keller also teaches mouse embryonic stem cells (EXAMPLE 1). Such cells may also be derived from, *inter alia*, humans (col. 6, paragraph 2).

Hence, at the time of invention, it would have been obvious to further modify the methods to use human ES cells, as Keller had shown such could be done with human ES cells

also. Moreover, the Artisan would expect success, as the cells were already known to develop into the various cell types as shown by Keller.

Claim Rejections – 35 USC § 103

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu/Leahy/Angelov/Tsung or Liu/Leahy/Angelov/Tsung/Keller as applied to claim 1, above, and further in view of U.S. Patent No. 5,143,854 to Pirrung.

As shown above, claim 1 is obviated by Liu/Leahy/Angelov/Tsung or Liu/Leahy/Angelov/Tsung/Keller, however none of the references teach or suggest the use of gene chip technology.

On the other hand, Pirrung teaches the use of such gene chip technology for the analysis of arrays of peptides for activity (ABSTRACT). Specifically, Pirrung teaches such technology is useful for, e.g., "[s]creening large numbers of polymers for biological activity" (e.g., col. 3, lines 39-41).

Moreover, one of ordinary skill in the art at the time of invention by Applicant would have found it obvious to modify the teachings by the use of gene technology as taught by Pirrung. The Artisan would have been motivated to do so because Pirrung allows for the controlled synthesis of a variety of polymers in a small space, which is particularly suited to the screening system described (ABSTRACT). Also, because both the references teach the various steps, and Pirrung has shown the gene chip technology successful, there exists a reasonable expectation of success.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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